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Sweeney

Title: Water-Soluble Thioester and Selenoester
Compounds and Methods of Making and
Using the Same

Appeal Brief

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In response to the final Office Action mailed April 13, 2009 and subsequent to the Notice of Appeal filed July 13, 2009, Applicants hereby submit the following Appeal Brief.

CERTIFICATE OF TRANSMITTAL UNDER 37 C.F.R. 1.8

I hereby certify that this paper (along with anything referred to as being attached or enclosed) is being electronically filed via EFS-Web at the United States Patent and Trademark Office, on the date shown below.

Oct. 9, 2009
Date of Deposit


Richard San Pietro

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Real Party in Interest

The real party in interest is the assignee of the case, Amylin Pharmaceuticals, Inc.

Related Appeals and Interferences

There are presently no other appeals or interferences pending that are related to this case.

Status of the Claims

Claims 60-72 are pending in the case and are on appeal. Applicant notes the Examiner rejoined claims 62, 64, 66, and 68-72 in the final Office Action mailed 4/13/09 (p. 2). Claims 1-59 have been canceled. Claims 73-74 are withdrawn.

Status of Amendments

No amendment of the claims after final rejection has been made.

Summary of Claimed Subject Matter

The present invention is directed to water-soluble thioester and selenoester compounds (specification, p. 2, lines 31-32). The thioester and selenoester compounds have the general structure of Formula I (specification, p. 16, line 24 and p. 19, lines 11-12). The compounds are characterized by an amino acid synthon joined to a water-soluble polymer through a thioester or selenoester (specification, p. 2, line 33 – p. 3., line 2). In Formula I, Y is selected from the group consisting of an amino acid, a peptide and a polypeptide (p. 17, line 3-4). X is sulfur or selenium (p. 16, line 28 – p. 17, line 1). n_1 and n_2 are each from 0 to 2, and n_3 is from 0 to 100 (p. 16, line 28). R and R_1 are individually selected from the group consisting of hydrogen, a side chain of an amino acid, a branched alkane, a cycloalkane, an alkyl-substituted aryl or heteroaryl group, and

combinations thereof (p. 17, lines 30-31; p. 19, lines 4-5). R₇ and R₈ are each, individually, selected from hydrogen, substituted and unsubstituted linear or branched chain alkyl, aryl, heteroaryl and benzyl (p. 19, lines 15-17). U is a linker or spacer and may be present or absent and, when present, consists of a linear or branched chain alkyl or heteroalkyl group of up to 18 carbon atoms (p. 19, lines 18-23). Polymer is a water-soluble polymer of a formula selected from the group consisting of: $-\text{C}(\text{O})-\phi-\text{C}(\text{O})-\text{NH}-\psi-\text{NH}-$ and $-\text{NH}-\psi-\text{NH}-\text{C}(\text{O})-\phi-\text{C}(\text{O})-$, where n₅ is an integer from 2 to 100 (p. 14, lines 9-16). ϕ and ψ are divalent radicals that may be the same or different (p. 14, line 15) and are selected from the group consisting of $-\text{((CH}_2\text{)}_{n_6}-\text{(CH}_2\text{CH}_2\text{O)}_{n_7}-\text{(CH}_2\text{)}_{n_6}-$ and $-\text{((CH}_2\text{)}_{n_6}-\text{(O-CH}_2\text{-CH}_2\text{)}_{n_7}-\text{(CH}_2\text{)}_{n_6}-$, where n₆ is an integer from 1 to 6 and n₇ is an integer from 2-50 (p. 14, lines 23-26). ϕ can also be $-\text{(CH}_2\text{-CH}_2\text{)-}$ and ψ can also be $-\text{(CH}_2\text{-(CH}_2\text{-CH}_2\text{-O)}_3\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{)-}$ or $-\text{(CH}_2\text{-CH}_2\text{-CH}_2\text{-(O-CH}_2\text{-CH}_2\text{)}_3\text{-CH}_2\text{)-}$ (p. 14, lines 27-28).

Grounds of Rejection to be Reviewed on Appeal

Whether claims 60-72 are unpatentable under 35 U.S.C. § 112, first paragraph as failing to comply with the written description requirement.

Argument

Claims 60-72 Stand Rejected Under 35 U.S.C. 112, first paragraph as Failing to Comply With the Written Description Requirement.

The Federal Circuit has indicated that the fundamental factual inquiry of the written description requirement is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed. See, e.g., *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). Possession may be shown in a variety of ways including description of an actual reduction to practice, or by

showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, e.g., *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997); *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it"). MPEP § 2163 I.

The Federal Circuit has also stated that a claim will not be invalidated on section 112 grounds simply because the embodiments of the specification do not contain examples explicitly covering the full scope of the claim language. *Falkner v. Inglis*, 448 F.3d 1357; 79 USPQ2d 1001 (Fed. Cir. 2006). The court stated that this is because the patent specification is written for a person of skill in the art, and such a person comes to the patent with the knowledge of what has come before. *Ibid*. Placed in that context, it is unnecessary to spell out every detail of the invention in the specification; only enough must be included to convince a person of skill in the art that the inventor possessed the invention and to enable such a person to make and use the invention without undue experimentation. *Id*.

The *Falkner* case involved an application claiming a vaccine against target viruses, specifically poxvirus, by using a viral vector to deliver proteins of the target virus to the inoculee. The viral vector contained genetic material of the target virus that, when injected into a human, produces harmless fragments of the target virus and confers immunity. In order to prevent the vector virus from itself causing a harmful infection, "essential genes" of the vector virus are deleted. The claim at issue recited these "essential genes" of the vector virus. The opponent to the application in an interference alleged that the written description requirement had not been satisfied because the application focused primarily on use of the technique on herpesvirus and, while mentioning poxviruses, indicated that no vaccine against poxvirus had yet been produced. But the BPAI found that the written description requirement had been satisfied.

On appeal the Federal Circuit agreed, explaining that expert testimony established that literature describing essential genes for poxvirus were well-known in the art, and that the skilled

person would have been readily able to choose an essential poxvirus gene based on references that were publicly available. Thus, in *Falkner* the Federal Circuit specifically held the following important principles:

- 1) examples are not necessary to support the adequacy of a written description;

With respect to this point the Federal Circuit stated “A claim will not be invalidated on section 112 grounds simply because the embodiments of the specification do not contain examples explicitly covering the full scope of the claim language. That is because the patent specification is written for a person of skill in the art, and such a person comes to the patent with the knowledge of what has come before. *Falkner*, (quoting approvingly from *LizardTech, Inc. v. Earth Resource Mapping, PTY, Inc.*, 424 F.3d 1336, 1345 (Fed. Cir. 2005). Thus, it is unnecessary to spell out every detail of the invention. Only enough must be included to convince a person of skill in the art that the inventor possessed the invention and to enable such a person to make and use the invention without undue experimentation. *Id.*

- 2) the written description standard may be met even where actual reduction to practice of an invention is absent;

With respect to this point the Federal Circuit re-affirmed that constructive reduction to practice is an established method of disclosure, and that an actual reduction to practice is not required to satisfy the written description requirement. *Id.*

- 3) there is no per se rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure.

With respect to this point, the Federal Circuit held that there is no per se rule that, whenever a claim limitation is directed to a macromolecular sequence, the specification must always recite the gene or sequence, regardless of whether it is known in the prior art. *Id.* Instead, where accessible literature sources clearly provided genes and their nucleotide sequences, satisfaction of the written description requirement does not require either the recitation or incorporation by reference of such genes and sequences. *Id.* This is consistent with other Federal Circuit holdings that what is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. See *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d at 1384, 231 USPQ at 94. See also *Capon v. Eshhar*, 418 F.3d 1349, 1357, 76 USPQ2d

1078, 1085 (Fed. Cir. 2005) ("The 'written description' requirement must be applied in the context of the particular invention and the state of the knowledge.... As each field evolves, the balance also evolves between what is known and what is added by each inventive contribution."). If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met. See, e.g., *Vas-Cath*, 935 F.2d at 1563, 19 USPQ2d at 1116; *Martin v. Johnson*, 454 F.2d 746, 751, 172 USPQ 391, 395 (CCPA 1972) (stating "the description need not be in *ipsis verbis* [i.e., "in the same words"] to be sufficient").

There is a strong presumption that an adequate written description of the claimed invention is present when the application is filed. *In re Wertheim*, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976). Consequently, the MPEP cautions that rejection of an original claim for lack of written description should be rare (emphasis added). MPEP § 2163 II.A.

Turning to the specific facts of the present case, in evaluating the claims the rejection (appropriately) considers factors such as the level of skill in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. While finding the level of skill in the art high (Office Action mailed 4/13/09, p. 5, line 2), and that partial structures are provided, the rejection nevertheless alleges that the claims lack written description, stating that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is not sufficient characteristic for written description purposes (Office Action mailed 4/13/09, p. 6, lines 2-5).

The logic of the rejection is misplaced and erroneous because, contrary to what is alleged in the rejection, the molecules of the invention are not described only by a functional characteristic. Indeed, a specific and limited core structure is provided in independent claim 60 with a reasonably limited constituents attached to that core, and the molecules are not claimed by their function at all. Thus, the rejection does not find support in the facts of the present case.

While acknowledging a written description for the two examples in the case, the rejection further alleges that there is insufficient description of a common core structure that would allow one of skill in the art to practice the invention as claimed (Office Action mailed 4/13/09, p. 6, lines 10-13). But claim 60, the sole independent claim, begins with recitation of a common core structure. The rejection stands against the clear pronouncements of the Federal Circuit, which has stated:

A claim will not be invalidated on section 112 grounds simply because the embodiments of the specification do not contain examples explicitly covering the full scope of the claim language. That is because the patent specification is written for a person of skill in the art, and such a person comes to the patent with the knowledge of what has come before. Placed in that context, it is unnecessary to spell out every detail of the invention in the specification; only enough must be included to convince a person of skill in the art that the inventor possessed the invention and to enable such a person to make and use the invention without undue experimentation.

Falkner, (quoting approvingly from LizardTech, Inc. v. Earth Resource Mapping, PTY, Inc., 424 F.3d 1336, 1345 (Fed. Cir. 2005)). A person of ordinary skill understands that the inventors possessed the claimed invention because, with the knowledge of the person of ordinary skill, can easily identify and make a large number of molecules within the breadth of the claim using the same chemical principles explained in the specification.

The rejection alleges “The variables of R , R_1 , R_7 , and R_8 , as well as the variance in n_1 and n_2 from 0 to 2, and n_3 from 0 to 100, does not allow for a core structure to inform one of ordinary skill in the art what is to be made.” (Office Action mailed 4/13/09, p. 6, lines 13-15). But again, a person of ordinary skill with resort to the specification, easily visualizes a large number of molecules within the claimed core structure and can readily make such structures using known chemical reactions. The variables n_1 and n_2 merely change the number of carbons in the chain, which is not at all a difficult task for a chemist of ordinary skill. The variable of n_3 is a repeating polymer of the same molecule structure, and also does not require more than the knowledge of the person of ordinary skill to visualize and implement in a variety of ways.

The rejection further alleges the “Polymer” is variant in structure. But again a specific and common core structure is provided for “Polymer” in the form of $-\text{C}(\text{O})-\phi-\text{C}(\text{O})-\text{NH}-\psi-\text{NH}-$ and $-\text{NH}-\psi-\text{NH}-\text{C}(\text{O})-\phi-\text{C}(\text{O})-$, where n_5 is an integer from 2 to 100, which is understood and easily applied by persons of ordinary skill with reference to the specification. The same is true for the element “U,” which is limited to linear or branched alkyls or heteroalkyls of up to only 18 carbon atoms. With resort to the specification chemists of ordinary skill readily visualize a variety of constituents that can be applied.

As acknowledged by the rejection (Office Action mailed 4/13/09 p. 6, lines 10-12) the present specification contains detailed examples of how to make and use molecules of the invention. Example 2 illustrates two protocols for construction of specific resins comprising a molecule of the invention. Example 3 describes the solid phase peptide synthesis of two specific peptides using principles of the invention, illustrating that the molecules of the invention function as expected. The person of ordinary skill understands that the same principles are applicable to an array of peptides and/or proteins and can readily apply such knowledge with reference to the present disclosure. Example 4 describes the handling properties of the molecules of the invention and the advantageous qualities they offer, particularly with respect to enhanced solubility of the reagents used in the known technique of native chemical ligation. Example 5 applies the principles of the invention in the synthesis of another peptide of the invention, and Example 6 describes the advantageous handling properties.

These Examples provide an actual reduction to practice of the claimed invention and the Supreme Court has held that an actual reduction to practice is a legal written description of a claim. *Pfaff v. Wells Elecs.*, 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998). Thus, the written description requirement is satisfied for this reason alone.

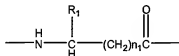
The principles of the invention are easily applied to almost any peptide or protein that can be synthesized using the known chemical technique of solid phase peptide

synthesis (SPPS). As is common in the chemical arts, an inventive principle once described can be easily applied to a broad array of similar molecules. Thus, it is both fair and to be expected that many constituents are encompassed by the claims. Consistent with *Falkner* and other statements of the Federal Circuit, this does not indicate that the written description standard is not met, merely that the principle is broadly and readily applicable once elucidated. This is easily understood by persons of ordinary skill in the art with resort to a disclosure.

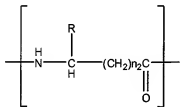
But one need not go to the examples to find a written description of the claimed invention in the present case. At p. 36 of the specification, structure 13 provides a written description of independent claim 60, as follows:

Claim

Y



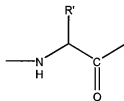
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X

Specification

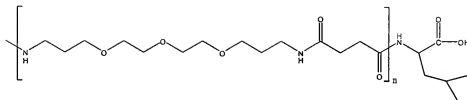
Y



S



U



-Polymer

Even though the Examiner acknowledged a written description for “Polymer” (Office Action mailed 4/13/09, p. 8, lines 3-9) the following paragraph will point out the basis for its written description for completeness, as follows:

It is first pointed out that the elements reciting group members of ϕ and ψ are recited as “selected from the group consisting of,” and thus any member of the group is within the scope of the claim. Additional possibilities specifically for ϕ and ψ individually are also recited at the end of the claim element. Taking $-(NH-\psi-NH-C(O)-\phi-C(O))_n$ as “polymer” in the example its components are then ψ is $-(CH_2-(CH_2-CH_2-O)_3-CH_2-CH_2-CH_2)-$, which is a specifically listed possibility in the claim, and literally supported at p. 14, line 28 of the specification. Then filling in the remaining $-NH-C(O)-$ of “polymer” in the claim, unit ϕ will be $-(CH_2-CH_2)-$, also a specifically listed possibility in the claim and literally supported at p. 14, line 27 of the specification. The C=O of Structure 13 then completes “polymer.”

It is therefore seen that Structure 13 of the claim does indeed provide a written description of claim 60 and is well supported in the specification. The same can be done for Schemes 4 and 5 on pp. 37 and 38 of the specification. The synthesis of the same structure is also shown in Example 2 and is used in Examples 3 and 5 to synthesize various bioactive peptides. Persons of ordinary skill also recognize that chemical molecules are easily manipulated to closely related structures without comprising the intended function of the molecule. Thus, courts have recognized that what is conventional or well known to one of ordinary skill in the art need not be disclosed in detail, as the Federal Circuit acknowledges that the person of skill in the art comes to the patent with a knowledge of what has come before, and

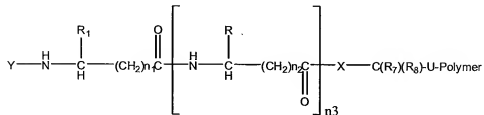
it is unnecessary to spell out every detail of the invention: only enough must be included to convince a person of skill in the art that the inventor possessed the invention and to enable such a person to make and use the invention without undue experimentation. *Falkner*.

Applicant has endeavored to be very specific in demonstrating that indeed an appropriate written description has been provided for the claimed invention, involving specific structural disclosures supported by actual examples. Since the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as claimed, the written description requirement is satisfied.

For all of the above reasons, the standard of the written description requirement as announced by the Federal Circuit is met.

Claims Appendix

60. A water-soluble thioester or selenoester compound of the formula:



wherein Y is selected from the group consisting of: an amino acid, a peptide, and a polypeptide;

X is sulfur or selenium;

n_1 and n_2 are each from 0 to 2, and n_3 is from 0 to 100;

R and R_1 are individually selected from the group consisting of: hydrogen, a side chain of an amino acid, a branched alkane, a cycloalkane, an alkyl-substituted aryl or heteroaryl group, and combinations thereof;

R_7 and R_8 are each, individually, selected from hydrogen, substituted and unsubstituted linear or branched chain alkyl, aryl, heteroaryl and benzyl;

U is a linker or spacer and may be present or absent and, when present, consists of a linear or branched chain alkyl or heteroalkyl group of up to 18 carbon atoms;

Polymer is a water-soluble polymer of a formula selected from the group consisting of: $-[C(O)-\phi-C(O)-NH-\psi-NH]_{n_5}$ and $-[NH-\psi-NH-C(O)-\phi-C(O)]_{n_5}$, where n_5 is an integer from 2 to 100, and

ϕ and ψ are divalent radicals that may be the same or different and are selected from the group consisting of $-((CH_2)_{n_6}-(CH_2CH_2O)_{n_7}-(CH_2)_{n_6})-$ and $-((CH_2)_{n_6}-(O-CH_2-CH_2)_{n_7}-(CH_2)_{n_6})-$, where n_6 is an integer from 1 to 6 and n_7 is an integer from 2-50, and where ϕ can also be $-(CH_2-CH_2)-$ and ψ can also be $-(CH_2-(CH_2-CH_2-O)_3-CH_2-CH_2-CH_2)-$ or $-(CH_2-CH_2-CH_2-(O-CH_2-CH_2)_3-CH_2)-$.

61. The thioester or selenoester compound according to claim 60 wherein Y is a peptide or polypeptide.

62. The thioester or selenoester compound according to claim 61 wherein said peptide or polypeptide comprises protected amino acids.

63. The thioester or selenoester compound according to claim 61 wherein said Y contains an N-terminal amino acid containing a group that supports chemical ligation.

64. The thioester or selenoester compound according to claim 60 wherein

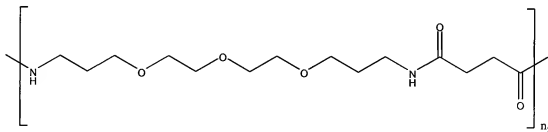
R_3 comprises a group of the formula $-C(R_7)(R_8)-U$ -Polymer, where

R_7 and R_8 are each individually selected from the group consisting of: hydrogen or linear, branched, substituted, or unsubstituted alkyl, aryl, heteroaryl, and benzyl, and

U is selected from the group consisting of alkyl, aryl, heteroalkyl, heteroaryl, alkoxy, of up to 18 carbon atoms, and

Polymer is selected from the group consisting of: $-[C(O)-\phi-C(O)-NH-\psi-NH]_{n_5}$ and $-[NH-\psi-NH-C(O)-\phi-C(O)]_{n_5}$, where n_5 is an integer from 1 to 100, and ϕ and ψ are divalent radicals selected from the group consisting of $-((CH_2)_{n_6}-(CH_2CH_2O)_{n_7}-(CH_2)_{n_6})-$ and $-((CH_2)_{n_6}-(O-CH_2-CH_2)_{n_7}-(CH_2)_{n_6})-$, where n_6 is an integer from 1 to 6 and n_7 is an integer from 2-50.

65. The thioester or selenoester compound of claim 60 wherein Polymer comprises a divalent radical of having the structure:



where n_5 is an integer of from 2 to 12.

66. The thioester or selenoester compound of claim 64 wherein

ϕ is $-(\text{CH}_2-\text{CH}_2)-$ and ψ is $-(\text{CH}_2-(\text{CH}_2-\text{CH}_2-\text{O})_3-\text{CH}_2-\text{CH}_2-\text{CH}_2)-$ or $-(\text{CH}_2-\text{CH}_2-\text{CH}_2-(\text{O}-\text{CH}_2-\text{CH}_2)_3-\text{CH}_2)-$.

67. The thioester or selenoester compound of claim 60 wherein R is a group of the structure $-\text{C}(\text{R}_4)(\text{R}_5)(\text{R}_6)$,

where R_4 , R_5 , and R_6 each individually are selected from the group consisting of: hydrogen, linear, branched, substituted or unsubstituted alkyl, aryl, heteroaryl, and benzyl.

68. The thioester or selenoester compound of claim 64 wherein

Y is a peptide or polypeptide;

X is sulfur;

n_1 and n_2 are 0;

R_7 and R_8 are each individually selected from the group consisting of: hydrogen, $-\text{CH}_3$, and $-\text{CH}(\text{CH}_3)_2$.

69. The thioester or selenoester compound of claim 68 wherein:

n_5 is from 2 to 50, n_6 is from 1 to 3, n_7 is from 2 to 5; and

ϕ is $-(\text{CH}_2-\text{CH}_2)-$ and ψ is $-(\text{CH}_2-(\text{CH}_2-\text{CH}_2-\text{O})_3-\text{CH}_2-\text{CH}_2-\text{CH}_2)-$ or $-(\text{CH}_2-\text{CH}_2-\text{CH}_2-(\text{O}-\text{CH}_2-\text{CH}_2)_3-\text{CH}_2)-$.

70. The thioester or selenoester compound of claim 60 wherein Y comprises an N-terminal group that supports chemical ligation.

71. The thioester or selenoester compound of claim 70 wherein the N-terminal group comprises cysteine or selenocysteine.

72. The thioester or selenoester compound of claim 71 wherein the cysteine or selenocysteine is protected.

Evidence Appendix

None

Related Proceedings Appendix

None

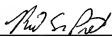
Closing

It is believed that the presently submitted claims are now in condition for allowance, and that this submission complies with all requirements. But if the Examiner or other PTO personnel have a question or concern that may be resolved quickly with a phone call, said persons are invited to contact the undersigned.

No fees are believed due with the filing of this paper that are not otherwise provided for herein, however, if any fee is or should become due or credit become payable during the pendency of these proceedings, the Examiner is authorized to charge or credit the same to **Deposit Account number 010535.**

Respectfully Submitted,

Dated: Oct. 8, 2009



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